



Ambient temperature and age-related notified *Campylobacter* infection in Israel: A 12-year time series study

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ABSTRACT

Background: *Campylobacter* spp. are the leading cause of foodborne infection worldwide, with a seasonal disease peak that might be affected by temperature increase. We studied the relationship between ambient temperature and weekly notified *Campylobacter* spp. infections.

Methods: Data on 29,762 laboratory-confirmed cases of *Campylobacter* infection for the period, January, 1999 to December, 2010 were retrieved from the Ministry of Health registry. To estimate the association between the number of weekly cases of *Campylobacter* infection and the national average temperature at lags 0–3 weeks, firstly, we used GAM models, and secondly two-segment piecewise linear Poisson regressions. The effect of temperature was adjusted for seasonality, long-term trends and holidays.

Results: We found a J-shaped relationship between ambient temperature and notified *Campylobacter* spp. cases. For *C. jejuni* in all ages, the curve below the threshold was constant and the percent increase in cases for 1 °C above a threshold of 27 °C was 15.4% (95%CI: 6.7–24.1%). For ages 3–10 yr and > =26 yr the curve was constant below the threshold and positive above it; the percent increase in cases for 1 °C was 17.7%(95%CI: 6.0–29.4%) and 23.7%(95%CI: 11.6–35.8%), respectively. For ages 0–2 yr the curve was linear with no threshold and the percent increase for 1 °C was 5.1%(95%CI: 2.1–8.1%). For ages 11–25 yr the curve was always constant. Results for *C. coli* were similar.

Conclusion: Our findings indicate that higher temperatures throughout the year affect *Campylobacter* spp. morbidity, especially in younger children. This should be taken into consideration in public education and health system preparedness for temperature increases as a result of climate change.

1. Introduction

Campylobacter species have emerged as leading bacterial causes of gastroenteritis and foodborne infections in developed countries since 1970 (EFSA (European Food Safety Authority), 2017). The annual incidence rates vary between 13/100,000 population in the United States (US), 71/100,000 population in the European Union, and 150/100,000 population in New Zealand (EFSA (European Food Safety Authority), 2017; The Institute of Environmental Science and Research Ltd, 2017; Crim et al., 2015). In Israel, the annual incidence rates of notified *Campylobacter* infections increased from 31 to 91/100,000 population between 1999 and 2010 and mostly affect toddlers younger than 2

years old (Weinberger et al., 2013). The vast majority of human infections are caused by 2 serotypes: *Campylobacter jejuni* and *Campylobacter coli*, which are responsible for 80–90% and 10–20% of infections, respectively (EFSA (European Food Safety Authority), 2017).

Symptoms of gastroenteritis due to *Campylobacter* infection usually persist for 3–4 days but may last for more than 1 week. The usual presentations include diarrhea, fever and abdominal pain. Late but rare complications include Guillain-Barré and hemolytic uremic syndrome. Chronic sequelae are more common and include reactive arthritis and irritable bowel syndrome (Allos et al., 2015; Keithlin et al., 2014). The incubation period in the majority of cases is fewer than 6 days, but may last up to 10 days (Horn and Lake, 2013).

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All age groups are affected, but the highest incidence is reported in children under 5 years (EFSA (European Food Safety Authority), 2017; Allos et al., 2015). In Israel the age-specific annual incidence rate during 1999–2010 forms an asymmetric U-shaped curve; with the highest rates in the first and second years of life (363 and 349/100,000, respectively), the lowest rate in the fifth decade of life (13/100,000), and a slight increase that occurs toward the eighth decade of life (26/100,000) (Weinberger et al., 2013).

The incidence of campylobacteriosis varies seasonally and geographically in temperate regions, and tends to be highest during the summer months in several countries (Nylen et al., 2002; Tam et al., 2006) including Israel (Bassal et al., 2016a). The temperature may directly affect the rate of replication of pathogens and their survival in the environment. In the absence of any control measures, increased ambient temperatures may therefore increase bacterial contamination at various points along the food chain. Ambient temperatures may also influence people's behaviour which, in turn, may be translated into more risky patterns of food consumption. For example, higher temperatures may lead to increased consumption of raw foods such as fruits and salads, and higher temperatures may encourage riskier cooking practices such as barbecuing (Kovats et al., 2005; Lake et al., 2009). Finally, in colder countries warmer temperatures may lead to increased outdoor recreational activity, which may make it more likely that people will be exposed to environmental sources of the relevant gastrointestinal pathogens (Lake et al., 2009).

Several epidemiological studies have demonstrated positive associations between temperature and *Campylobacter* spp. infection in England and Wales (Lake et al., 2009) Brisbane, Australia (Bi et al., 2008) and in Alberta and Newfoundland-Labrador in Canada (Fleury et al., 2006), accounting for seasonality using different modeling approaches.

It is not certain whether the results from those studies can be applied to other ecological/meteorological regions, given various population characteristics, eating behaviors, food processing chains, socioeconomic status and climate types.

We aim to evaluate the age-related relationship between ambient-temperature and weekly notified *Campylobacter* spp. cases using time-series analysis in Israel, a country with Mediterranean climatic conditions and a high incidence of infection. The majority of the Israeli population reside in regions that have a Mediterranean climate.

2. Materials and methods

2.1. Surveillance data

Campylobacteriosis is a reportable disease in Israel. Microbiology laboratories throughout the country passively submit all isolates of *Campylobacter* spp. to the *Campylobacter* Reference Center, Israeli Ministry of Health, Jerusalem, for confirmation, final identification and further classification. The registry completeness of *Campylobacter* spp. cases is about 90%. Demographic data on 29,762 laboratory-confirmed cases of *Campylobacter* infection among the Jewish population during the period, 1st January, 1999 to 31st December 2010 were obtained from the *Campylobacter* Reference Center. During the study period, there were no changes in the reporting practices and no interventions to control the disease. The date of each *Campylobacter* case was the date on which the specimen was submitted for culture in the reporting Microbiology laboratory. The delay between the disease onset and the submission of stool culture for testing is estimated at a median of 5–7 days based on a recent study from Israel (Ziv et al., 2011). Therefore, the reporting date was a reasonable indicator of disease's onset date, with an approximate 1-week delay. In order to achieve maximal homogeneity of the study population, only the Jewish population was included; during the study years, this accounted for 78.8% (1999) to 75.1% (2010) of the total population in Israel. Weekly cases of *Campylobacter* infection for the serotypes *C. jejuni* and *C. coli* and for 4 age

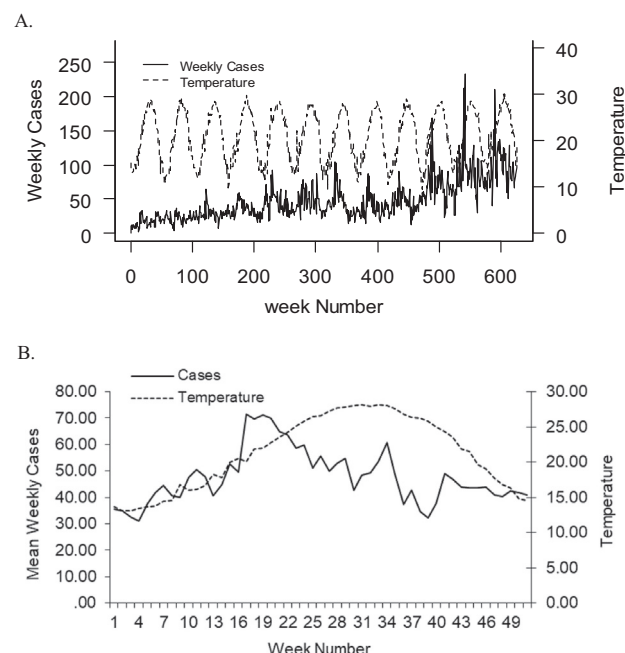


Fig. 1. Patterns of weekly total number of *Campylobacter* infection cases (—) and weekly mean temperature in °C (---) during the period, 1st January, 1999 to 31st December, 2010; A) The study weeks in a sequential order (n = 1–626), B) The study weeks in a year (n = 1–52). Note: the Israeli week is Sunday-Saturday hence the first two observations were omitted.

groups were calculated for the whole study period (626 weeks).

2.2. Meteorological data

The national temperature and relative humidity series were constructed using daily data from the weather climate station in Ben Gurion Airport (in the center of the country) obtained from the Israeli meteorological office archive. The mean temperature and relative humidity for each week were calculated and the weekly changes in this station represent quite well the changes across the country.

2.3. Statistical methods

We modeled the effect of temperature on the weekly number of cases (dependent variable) in two steps, assuming Poisson distribution with over-dispersion. Models were controlled for the following variables: holidays (number of days per week 1–7; typically, the number of cases are low during holidays and high immediately afterward; week number (1–626, to control for long-term effect); seasonality (Fourier terms, up to the second harmonic, were included). First, to explore the shape of the relationship, we fitted and graphed a Poisson Generalized Additive Model (GAM) model with a penalized natural cubic spline of weekly temperature. The degree of smoothness of model terms was estimated as part of the fitting. Smooth terms were represented using penalized regression splines with smoothing parameters selected by Generalized Cross Validation (GCV) or Akaike Information Criterion (AIC) (Kovats et al., 2004). Secondly, in order to quantify the relationship, we fitted a two-segment piecewise linear regression model (Kovats et al., 2004) under which it was assumed that there are different linear effects of temperature until a threshold value is reached, and afterward. The temperature threshold was estimated by maximum likelihood from among thresholds across all integer values of the temperature measure (Muggeo, 2003). Likelihood-profile confidence intervals were calculated from these arrays of likelihood, scaled to allow for over-dispersion. If the threshold temperature was found to be a value lower than the P25 (the 25th percentile) or greater than the P75

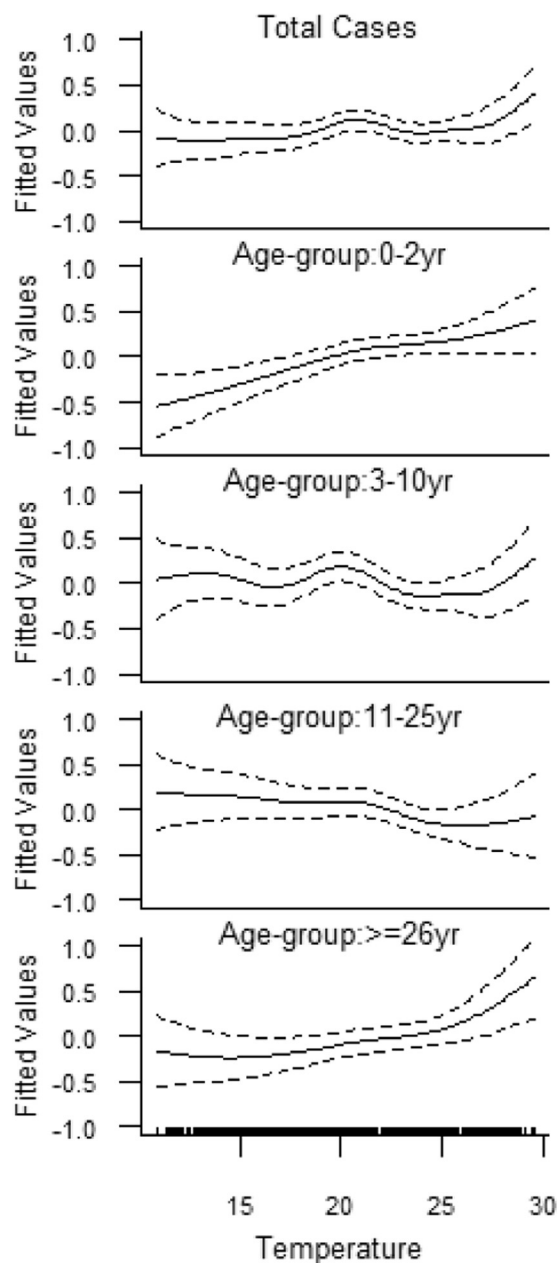
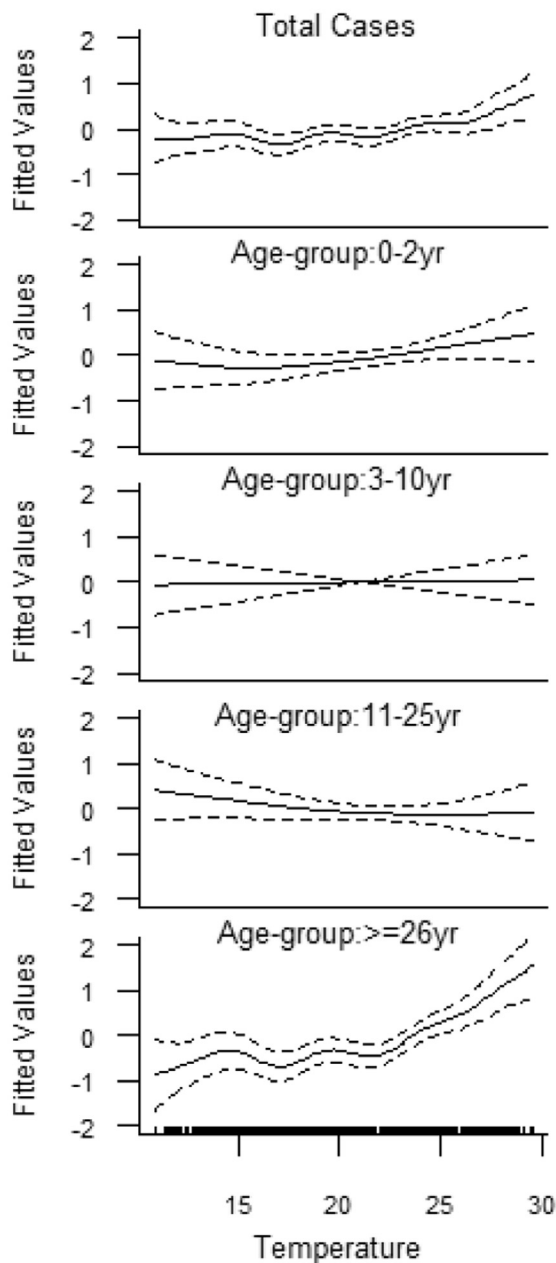
A. *C.jejuni*B. *C.coli*

Fig. 2. Temperature – *Campylobacter* infection relationship; results of GAM modeling.

(the 75th percentile) temperature measure distribution, we fitted in addition a linear model (a 1-segment model). For sensitivity analysis we fitted a 3-segment piecewise linear regression model, with two thresholds and 3 slopes. Exploratory analysis indicated that the delay between high temperature and increased number of cases where present, was not more than 3 weeks. Therefore, the temperature measure used in our models was a mean value of lags 0–3 weeks; this provided the combined effect of temperature from the previous month on the disease. We also investigated the effect of individual lags of weekly temperature entered separately to the model.

We stratified the analysis according to the *Campylobacter* spp. main serotype: *C. jejuni* and *C. coli*, and to 4 age groups, toddlers (0–2 years, 28% of cases), children (3–10 years, 25% of cases), teenagers and young adults (11–25 years, 22% of cases); and adults (≥ 26 years, 25% of cases). Primary analyses (results not shown) indicated that

relative humidity and other meteorological variables had no effect on *Campylobacter* infections, hence these were not included in the model. All analyses were conducted in R (R Development Core Team: A Language and Environment for Statistical Computing, version 2.13.0. 2011)

2.4. Ethical considerations

The study was approved by the local Ethical Committee of Assaf Harofeh Medical Center and the Ethical Committee of Tel Aviv University, Tel Aviv, Israel.

3. Results

Fig. 1 illustrates the seasonal patterns along the 12 study years of

Table 1

Temperature –*Campylobacter* infection relationship: Thresholds and slopes estimated in two-segment piecewise linear regression; by serotype and age-group.

Age-groups	Threshold (95%CI)	% change ^a per 1 °C under threshold (95%CI)	% change ^a per 1 °C above threshold (95%CI)
<i>C. jejuni</i>			
Total cases	27 (25.9, 27.7)	0.6 (–1.9, 3.0)	16.1 (7.2, 24.9)
0–2 yr	28 (27.2, 28.9)	6 (1.5, 7.7)	30.2 (2.3, 57.9)
3–10 yr	27 (25.9, 27.7)	– 2.1 (–5.5, 1.3)	19.2 (7.0, 31.5)
11–25 yr	21 (18.6, 23.7)	– 0.3 (–4.7, 4.1)	– 6.7 (–13.2, –0.1)
> = 26 yr	27 (25.9, 27.8)	1.9 (–1.6, 5.5)	23.2 (9.4, 36.9)
<i>C. coli</i>			
Total cases	27 (25.6, 28.1)	2.3 (–1.5, 6.2)	18.8 (4.8, 32.8)
0–2 yr	15 (13.7, 17.3)	– 11.7 (–25.2, 1.8)	10.5 (0.9, 13.9)
3–10 yr	13 (11.6, 15.0)	40.4 (–27.7, 196.2)	– 1.7 (–8.6, 5.1)
11–25 yr	26(24.3, 28.6)	3.0 (–1.7, 7.7)	21.5 (7.4, 33.2)
> = 26 yr	22 (20.6, 23.0)	– 4.1 (–10.3, 2.1)	12.4 (–7.6, 32.4)

^a In weekly cases of disease, for 626 weeks.

infection with *Campylobacter* spp., as well as temperature patterns where the weeks (1–626) are in a sequential order (Fig. 1a) or per year (Fig. 1b). We observed that the infection peak in late spring (week 20 which is at the end of May) occurred prior to the temperature peak. For further analysis, the temperature measure was a mean of lag0-lag3 (mean of 0–3 weeks preceding the case), with the following distribution: Median = 21.3 °C, P25-P75: 16.0–26.2 °C (P5-P95:13.0–28.1 °C).

Fig. 2 describes the fitted relationship between *Campylobacter* cases by serotype and temperature (mean lag0-lag3) based on GAM modeling, for total cases and stratified by age group. The centerline is the estimated spline curve, and the upper and lower lines represent the 95% upper and lower confidence limits, respectively. Based on those findings a two-segment linear regression was fitted and the results are presented in Table 1 and Fig. 3. For the total cases (all age groups) we found a J-shaped relationship between temperature and *Campylobacter* cases. For *C. jejuni*, the curve below the threshold was constant and the percent increase in cases for 1 °C above a threshold of 27 °C (P82 of the temperature distribution) was 16.1% (95%CI: 7.2–24.9%). Similar results were found for *C. coli*. Stratification by age-group yielded different patterns of relationships; the thresholds and the exposure-response curves varied between the 4 age-groups, as follows:

Age-group 0–2 yr: For *C. jejuni* and *C. coli* the thresholds were 28 °C (P95) and 15 °C (P20) respectively, both outside the P25-P75 range of the temperature distribution suggesting nonexistence of thresholds. Therefore linear models were fitted and we found that the percent increase in cases for 1 °C for *C. jejuni* was 5.1% (95%CI: 2.1–8.1%) and for *C. coli* – 2.9% (95%CI: –0.03 to 9.0%).

Age-group 3–10 yr: For *C. jejuni* and *C. coli* the thresholds were 27 °C (P82) and 13 °C (P5) respectively. For *C. jejuni* the curve was constant below the threshold and positive above it; and the percent increase in cases for 1 °C above the threshold was 19.2% (95%CI:7.0–31. 5%). For *C. coli* there was no threshold and the linear curve was found to be constant.

Age-group 11–25 yr: For *C. jejuni* and *C. coli* the thresholds were 21 °C (P45) and 27 °C (P82), with constant curves below the thresholds. For *C. jejuni* the percent decrease in cases for 1 °C above the threshold was – 6.7% (95%CI: –13.2 to –0.1%) and for *C. coli* the percent increase in cases for 1 °C above the threshold was 21.5% (95%CI: 7.4–33.2%).

Age-group > = 26 yr: For *C.jejuni* and *C. coli* the thresholds were 27 °C and 22 °C (P54) with constant curves below the thresholds and positive above it, and with similar slopes. The percent increase in cases for 1 °C above the threshold was 23.2% (95%CI: 9.4–36.9) for *C. jejuni* and 23.7% (95%CI: 13.2–34.2%) for *C. coli*.

Fig. 4 illustrates the percent change in cases associated with temperature measured on each separate week before disease onset, up to a

lag of 9 weeks. The greater effect of temperature was 0–3 weeks before the onset of the disease, with a diminishing but positive effect of up to 5 weeks. Sensitivity analysis using a mean-temperature of lag0-lag9 or lag0-lag5 instead of lag0-lag3 yielded similar results; and a 3-segment piecewise regression did not yield a better model performance than the two-segment piecewise regression.

by serotype and age-group. (A) *C. jejuni*, (B) *C. coli*. Temperature (°C) on the x-axis (0–3 week mean) and log rate ratio of *Campylobacter* infection on the y-axis. The center line is the fitted smoothed values for the temperature range and upper and lower lines are the 95% confidence intervals.

4. Discussion

We studied the association between ambient temperature and notified cases of *Campylobacter* infection in a Mediterranean climate type.

We found a significant positive temperature-disease relationship for the two prominent serotypes in Israel, *C. jejuni* and for *C. coli*; controlling for season, public holidays and long-time trends. Beyond a threshold temperature of 27 °C, a 1 °C rise was found to correspond to a 16.1% increase of reported *C. jejuni* infection cases and 18.8% *C. coli* cases.

Our results of a positive relationship between ambient temperature and notified cases of *Campylobacter* infection are consistent with research carried out in other countries with different weather conditions using time-series designs. A 1 °C rise in temperature was found to correspond to a 4.5% or 2.2% increase in Newfoundland–Labrador, Canada, and Alberta, Canada respectively, with a threshold temperature of 0 °C or – 10 °C (Fleury et al., 2006). In Brisbane, Australia, the increase was 0.9% (Bi et al., 2008). A 1 °C rise in temperature was found to correspond to a 5.3% increase in infection cases in England and Wales (Lake et al., 2009). Our results suggest a more pronounced temperature effect, which might be related to the local hot Mediterranean climate.

The J-shaped temperature-*Campylobacter* infection relationship showing a positive slope after a threshold temperature that was found in our study following GAM modeling is not unique to this infection. Similar patterns were found in a recent temperature-health epidemiological studies on ambient temperature-*Salmonella* infection relationship (Kovats et al., 2004) and in studies on temperature-mortality relationship (Baccini et al., 2008) which showed that temperature is a contributing factor for an increased risk of infection. Notably, higher thresholds were found in warmer climates for the temperature-mortality J-shaped relationships (Baccini et al., 2011).

These results clearly indicate that weather may be one of the contributing factors for *Campylobacter* infection. Temperature may impact on the growth of food-borne pathogens, animal reservoirs and host behaviors (Rose et al., 2001). It may affect the level of poultry contamination with *Campylobacter* spp., the eating habits and the type of food prepared in households (Bi et al., 2008).

We followed recent temperature-health studies using refined weekly notified cases of *Campylobacter* infection for studying the temperature effect. Daily data are usually too scarce to run appropriate analyses, and monthly data might not be able to provide up-to-date information for food-borne disease, and could be less sensitive in detecting climate impacts. We investigated the smallest length of accumulated lags needed to clarify temperature effect and found it to be up to 3 weeks. *Campylobacter* infections are foodborne, the main source being poultry consumption, both worldwide and in Israel (Weinberger et al., 2013, 2016; Bassal et al., 2016b; Wagenaar et al., 2013). Notably, the incubation period for *Campylobacter* gastroenteritis is roughly 1 week but may be even longer (Allos et al., 2015) and the delay in culture submission is 5–7 days (Ziv et al., 2011). Then we have to allow some more time for the purchase and preparation of the food item before consumption. Although *Campylobacter* spp. contamination may occur at any time-point, from farm to fork, the 4-week (lags 0–3) lag may

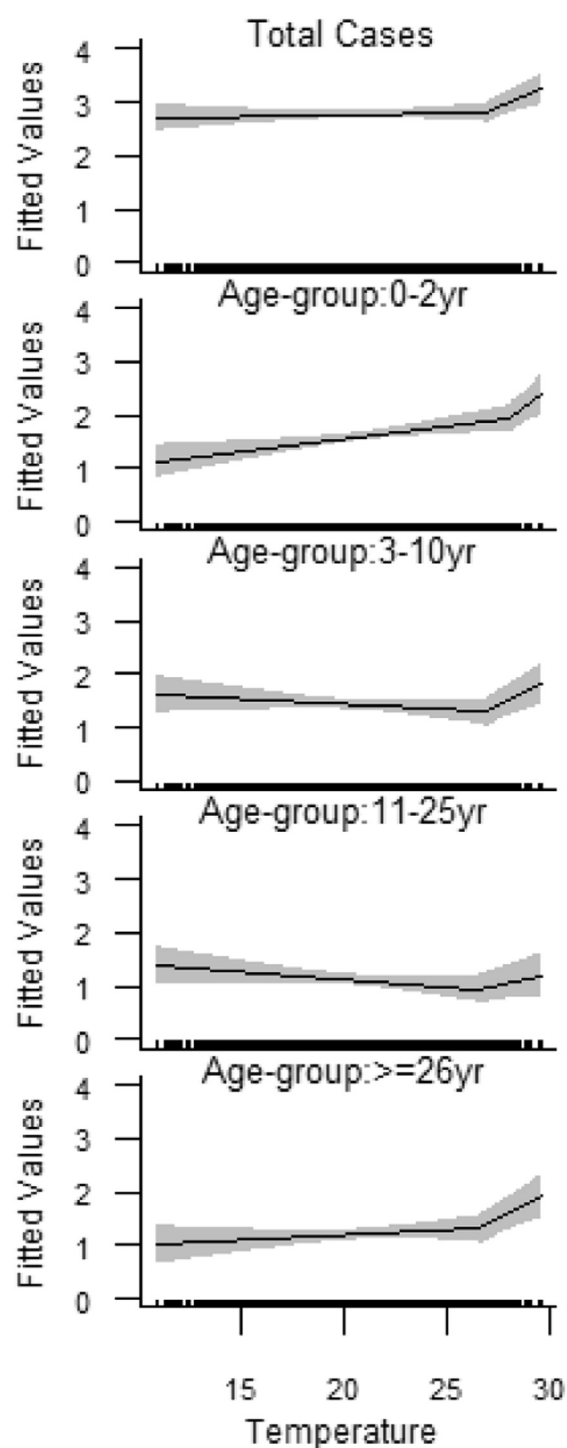
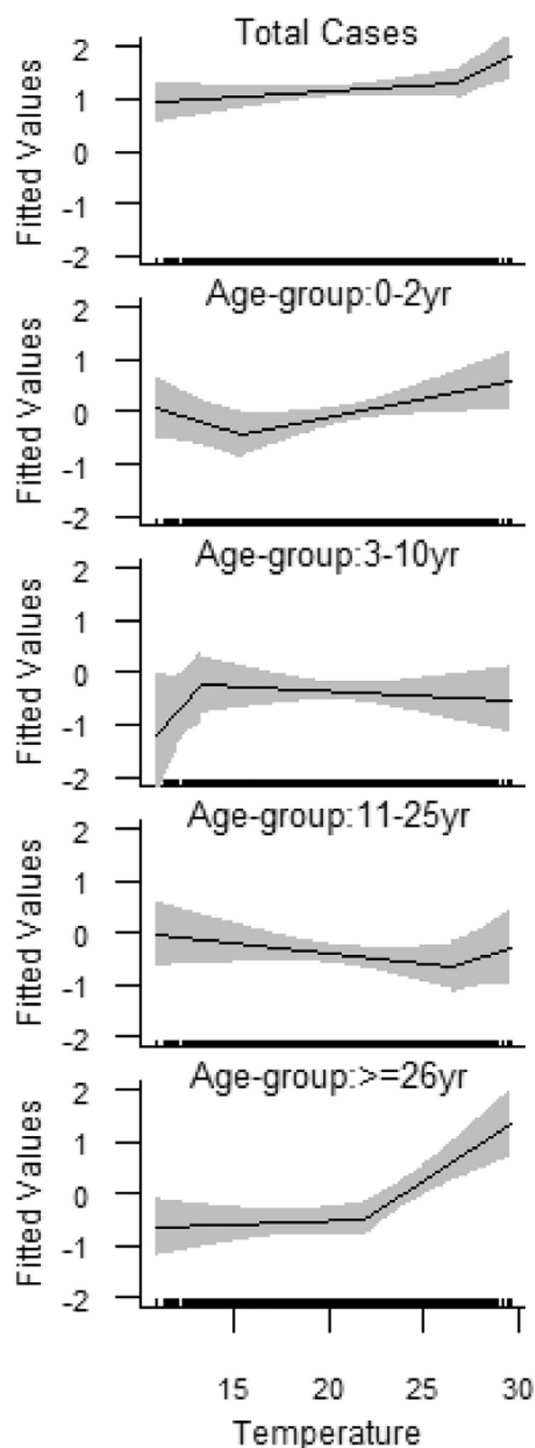
A. *C.jejuni*B. *C.coli*

Fig. 3. Temperature – *Campylobacter* infection relationship: Curves of 2-segment piecewise linear regression modeling (95%CI); by serotype and age-group. (A) *C. jejuni*, (B) *C. coli*. Temperature (°C) on the x-axis (0–3 week mean) and log rate ratio of *Campylobacter* infection on the y-axis. The center line is the fitted values for the temperature range including the intercept and upper and lower lines are the 95% confidence intervals.

suggest that temperature effect around purchasing time or somewhat earlier. Indeed, a recent Swiss study, using a time-series approach, found a positive direct correlation between *Campylobacter* spp. prevalence in broilers and *Campylobacter* infection in humans with a 2-week delay (Wei et al., 2015).

Similarly, in Denmark a positive temperature-*Campylobacter*

infection association was shown with a 4-week lagged effect (Patrick et al., 2004). In contrast, in the international study by Kovats et al. (2005) on the relationship between temperature and peak-time of *Campylobacter* infection, a lag of more than 2-months was reported. The lag time could vary in different areas depending on local weather conditions and food processing and longer lags could indicate the

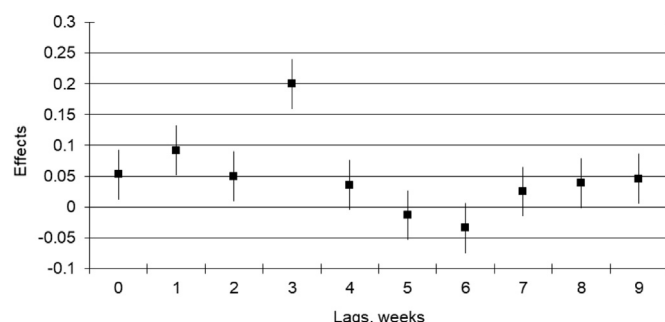


Fig. 4. Temperature – *Campylobacter* infection relationship; the effect of temperature for each week-lag between disease onset and temperature exposure (% change) for temperature above a threshold (27 °C).

significance of the conditions earlier in the food production process, e.g. animal husbandry and slaughtering or processing and distribution, rather than the importance of food storage and hygiene close to the point of consumption (Bi et al., 2008). Further studies including more local influencing factors, such as socio-economic status and public health services, would be important to fully understand the causes of the various effects of weather variables on *Campylobacter* infection.

An age-related approach to ambient temperature- *Campylobacter* infection relationship was not previously applied to this infection, despite the well-characterized differences in incidence trends of this infection. Age-stratified analyses in our study found different patterns (threshold and slope) between the 4 age-groups. For *C. jejuni* incidence, age-group 0–2 yr appeared to be the most sensitive to temperature effect with no obvious temperature threshold; age groups 3–10 yr and > =26 yr appeared to be sensitive to high temperature effect; age group 11–25 yr appeared to be non-sensitive to temperature.

The unique pattern in age group 0–2 years can be explained by a higher sensitivity to *Campylobacter* infection due to the toddlers' immature immune system. In a country with a high level and persistent exposure to *Campylobacter* spp., older age groups may develop immunity to the infection, which can mitigate the rate of infection (Weinberger et al., 2013). Thus they will develop clinical infection only when the level of *Campylobacter* spp. exposure load is above a certain threshold. Additional explanation may be a different source of infection for this young age group. Handling and consumption of contaminated chickens is considered the major route for *Campylobacter* infection (EFSA Panel on Biological Hazards BIOHAZ, 2011). While it is less likely that toddlers of younger than 2 years old handle or consume undercooked chicken, they may be susceptible to cross contamination in the household or even horizontal transmission from a sick older person in the household where chickens are consumed (Bassal et al., 2016b). Exposure to pets may also play an important role in these age groups (Buettner et al., 2010).

There are limitations in the use of national passive surveillance data. Not all cases in the community are represented in such a data set. But there is no reason to believe that the degree of underreporting varies over time; nor is there reason to believe that the reporting varies during the weeks of the year (e.g. more in hot weeks) and therefore our results seem to be valid. In addition the national surveillance data do not include any clinical data and infection encountered outside the country via travelling could not be excluded but since the percent of illness due to travelling is low this might not bias our results. Delay between disease onset and submission of stool for culture is estimated in Israel at as 5–7 days

We used the weather station in the national airport in the center of Israel to represent the whole country temperature weekly changes during the study period. Since the majority of the Israeli population reside in the center of the country (characterized with a Mediterranean climate) this limitation probably has a minor influence on the results.

5. Conclusion

Our findings of a J-shaped temperature-disease relationship are in line with other studies, albeit with an increased threshold temperature. Higher temperatures across seasons, prior to or around the time of food purchasing, probably play a role in human infection. Notably, the age-related exposure-response curves varied between the age groups, with the age group 0–2 yr being the most affected. Effective interventions should target this age group.

Temperatures are rising due to global climate change, and more weeks with the above-threshold temperature are expected to occur (Zittis et al., 2015). Without effective interventions, it is likely that temperature-effect on *Campylobacter* infection incidence may be even higher. *Campylobacter* foodborne illnesses should be considered in the adaptation and preparedness plans for temperature increase as a result of climate change, with a special focus on the very young age groups.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Ethical considerations

The study was approved by the local Ethical Committee of Assaf Harofeh Medical Center and the Ethical Committee of Tel Aviv University, Tel Aviv, Israel

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